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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/301,380	06/15/2001	GERALD P. MURPHY	20093A-002100US	5494

20350 7590 11/23/2001

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EXAMINER

SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 11/23/2001

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/301,380

Applicant(s)

MURPHY ET AL.

Examiner

Mary Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 2,14,15,18,20 and 21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,3-13,16,17 and 19 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s) ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: _____

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DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1, 3-13, 16-17 and 19, in Paper No. 15 is acknowledged.
2. Claims 2, 14-15, 18 and 20-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 16 are indefinite since they claim subject matter not elected in the present invention, antisense to Nr-CAM and methods of using said antisense. For instance, the claim limitations specifying Nr-CAM antibodies are not embraced within the elected group.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-13, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the specific antisense (claimed by SEQ ID NO.) to Nr-CAM taught in the specification as filed and methods of administration of the disclosed antisense via injection to the specific glioblastoma tumors taught by way of example, does not reasonably provide enablement for any inhibitory molecule to any Nr-CAM from any species nor any method of use of such molecules in any whole organism for therapeutic purposes as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a pharmaceutical composition for the inhibition or treatment of tumorigenesis comprising an antisense nucleic acid complementary to at least a portion of an RNA transcript of a Nr-CAM gene in an amount effective to inhibit hyperproliferation of a tumor cell. Claim 3 is drawn to a method of treating, inhibiting or preventing a disease or disorder involving cell overproliferation in a subject comprising administering to a subject in which such treatment or prevention is desired an effective amount of a molecule that inhibits Nr-CAM function. Claims 4-11 add the following limitations: (1) in which the disease or disorder is a malignancy; (2) in which the disease or disorder is selected from the group consisting of brain cancer, leukemia and B cell lymphoma; (3) in which the subject is a human; (4) in which the brain

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cancer is selected from the group consisting of glioblastoma, glioma, meningioma, astrocytoma, medulloblastoma, neuroectodermal cancer and neuroblastoma; (5) in which the glioblastoma is glioblastoma multiforme; (6) in which the disease or disorder is selected from the group consisting of premalignant conditions, benign tumors, hyperproliferative disorders, and benign dysproliferative disorders; (7) in which the molecule that inhibits Nr-CAM function is (modified claim 10) a Nr-CAM antisense nucleic acid; and (8) in which the molecule that inhibits Nr-CAM function is an oligonucleotide which (1) consists of at least six nucleotides; (b) comprises a sequence complementary to at least a portion of an RNA transcript of a Nr-CAM gene; and (c) is hybridizable to the RNA transcript under moderately stringent conditions.

Claim 12 is drawn to a method of inhibiting, treating or preventing a disease or disorder involving cell proliferation in a subject comprising administering to a subject in need of such treatment an effective amount of a molecule that promotes Nr-CAM function. Claim 13 further specifies in which the disease or disorder is selected from the group consisting of degenerative disorders, growth deficiencies, hypoproliferative disorders, physical trauma, lesions, and wounds. Claim 17 is drawn to a pharmaceutical composition for the inhibition or treatment of tumorigenesis comprising an antisense nucleic acid complementary to at least a portion of an RNA transcript of an Nr-CAM ligand encoding gene in an amount effective to inhibit hyperproliferation of a tumor cell. Claim 19 is drawn to a method of inhibiting, treating or preventing a disease or disorder involving cell overproliferation in a subject comprising

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administering to a subject in which such treatment or prevention is desired an effective amount of a molecule that inhibits an Nr-CAM ligand encoding gene function.

The claims broadly read on design of any antisense to any Nr-CAM from any species for administration to any whole organism for therapeutic purposes. The specification as filed teaches by way of example administration of pCMV1/3Nr-AS and pCMV1/3Nr-AS to mice glioblastomas and reduction of the tumor volume to no tumor. The specification as filed is enabling for administration of these antisense to glioblastomas by way of injection, but such results do not correlate to the breadth of the claimed invention for treatment of any tumor cell, by any means of administration with any molecule that inhibits Nr-CAM ligand encoding gene function.

Specifically, the lack of correlation for the breadth claims stems from the fact that there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically

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important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Furthermore, while the specification as filed teaches administration of specific antisense to Nr-CAM, such results do not correlate to antisense to any region of any species of Nr-CAM for any routes of administration as broadly claimed.

One of skill in the art would not accept on its face the successful delivery of any Nr-CAM antisense molecule *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art of the unpredictable factors argued above. Specifically the specification does not teach (1) stability of any Nr-CAM antisense molecules *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues by routes other than direct injection into the tumor, (3) dosage and toxicity of inhibitory molecules

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administered by any other route of administration than direct injection, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects of any inhibitory molecule of Nr-CAM administered by any route of administration. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Moscoso et al. (J. Of comparative neurology, Feb. 13, 1995, 352 (3), p. 321-34.).

Claim 16 is drawn to a kit comprising in one or more containers a molecule selected from the group consisting of an anti-Nr-CAM antibody, a nucleic acid probe capable of hybridizing to a Nr-CAM RNA, a pair of nucleic acid primers capable of priming amplification of at least a portion of a Nr-CAM nucleic acid, an anti-Nr-CAM ligand antibody, a nucleic acid probe capable of

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hybridizing to an Nr-CAM ligand encoding RNA and a pair of nucleic acid primers capable of priming amplification of at least a portion of an Nr-CAM encoding nucleic acid.

Moscoso et al. teach primers to Nr-CAM used for cloning alternate splice forms of murine L1-related CAM and putative murine orthologs of the chicken cell adhesion molecules Nr-CAM (see abstract).

Moscoso et al. thus anticipate the claimed invention.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
November 8, 2001



ANDREW WANG
PRIMARY EXAMINER